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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Lawrence J. Marnett

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06/23/2006

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NASHVILLE, TN 37219-2376

EXAMINER

PAK, YONG D

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 06/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/924,082	Applicant(s) MARNETT ET AL.	
	Examiner Yong D. Pak	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 May 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4,6-43 and 49-62 is/are pending in the application.
- 4a) Of the above claim(s) 22-43 and 49-54 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4,6-21 and 55-62 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 5, 2006, canceling 2-3, 5 and 44-48, amending claims 4, 6, 8, 13 and 14, and adding claims 55-62, has been entered.

Claims 4, 6-43 and 49-62 are pending. Claims 22-43 and 49-54 are withdrawn. Claims 4, 6-21 and 55-62 are under consideration.

Response to Arguments

Applicant's amendment and arguments filed on May 6, 2006, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

Claims 56 and 60 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s)

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in proper dependent form, or rewrite the claim(s) in independent form. Not all the recited disease states are "inflammation" diseases and therefore, do not further limit the "inflammation" disease states of claims 55 and 59..

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 6 and 13 and claims 7-12, 14-21 and 59-62 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 6 and 13 recite the phrase "measuring an activity of a COX-2 enzyme in a living subject". The metes and bounds of the phrase in the context of the claims are not clear. It is not clear to the Examiner as to how those skilled in the art "measure activity of COX-2 enzyme in a living subject". This is because in the claims only recite steps of measuring PGH₂-EA in a sample. Therefore, the method lacks essential step(s).

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 recites the phrase "relating the amount of the PGH₂-EA metabolite to the activity of the COX-2 enzyme in the subject". The metes and bounds of the phrase in the context of the claim are not clear. This is because the claims only recite steps of measuring PGH₂-EA in a sample and it is not clear to the Examiner how one of skill in the art "relates" the amount of the PGH₂-EA metabolite to the activity of the COX-2 enzyme in the subject, and thereby measuring COX-2 activity in a "living subject". Therefore, the method lacks essential step(s).

Claim 6 and claims 7-12 and 55-58 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the phrase "detecting an amount of a PGH₂-EA metabolite in the sample, wherein the presence of the PGH₂-EA metabolite in the sample indicates the activity of the COX-2 enzyme in the subject". The metes and bounds of the phrase in the context of the claims are not clear. It is not clear to the Examiner as to how those skilled in the art can conclude that COX-2 activity in the subject is measured by detecting PGH₂-EA metabolite in the sample. This is because applicants have not set up any control steps in which the amount of PGH₂-EA metabolite that are produced naturally in the absence of COX-2 activity are taken into consideration. Therefore, the method lacks essential step(s).

Claims 6 and 13 and claims 7-12, 14-21 and 55-62 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6 and 13 recite the phrase "relating the detected amount (of COX-2 activity) to a disease state or the progression of a disease state". The metes and bounds of the phrase in the context of the claims are not clear. It is not clear to the Examiner as to how those skilled in the art "relates the amount of COX-2 activity to a disease state or the progression of a disease state". This is because in the claims only recite steps of measuring amount of PGH₂-EA metabolite in a sample and it is not clear to the Examiner how one of skill in the art "relates" the amount of COX-2 activity to a disease state or the progression of a disease state. Therefore, the method lacks essential step(s).

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 4 is rejected under 35 U.S.C. 102(b) as being anticipated by Yu et al.

Claim 4 is drawn to a method of measuring activity of COX-2 by obtaining a sample from a living subject, quantifying an amount of PGH₂-EA metabolites and relating the amount of the metabolites to the activity of the COX-2 in a subject.

Yu et al. (Reference BN: PTO-1449) teaches a method of detecting/measuring COX-2 in a sample derived from a mammalian cell, which is a "living subject", by detecting/measuring a PGH₂-EA metabolites (Figures 2-6 and pages 21182). Arachidonyl ethanolamide (AEA), a precursor for PGH₂-EA metabolites is not a substrate for COX-1 and therefore, the method of Yu et al. only selectively detects COX-2 activity (page 21182, right column, page 21183, right column, page 21184, right column and page 21186, left column). The method of Yu et al. "relates the amount of PGH₂-EA metabolites to the activity of the COX-2 enzyme in the subject", since detection and quantification of PGH₂-EA metabolites is indicative of COX-2 activity. Therefore, the teachings of Yu et al. anticipate claim 4.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants should note that the rejection has been amended in light of the amendment of the claims.

Applicants argue that Yu et al. fail to disclose or suggest a method of direct detection from a sample of a subject to determine activity of a COX-2 enzyme. Examiner respectfully disagrees. The claims do not recite the limitation of "direct detection from a sample". Rather, the claims are drawn to a method of measuring activity of COX-2 by detecting/measuring PGH₂-EA metabolites. Yu et al. does teach a method of detecting/measuring activity of COX-2 by detecting PGH₂-EA metabolites (Figures 2-6 and page 21182, right column, page 21183, right column, page 21184, right column and page 21186, left column). Since Yu et al. teaches that arachidonyl ethanolamide (AEA), a precursor for PGH₂-EA metabolites is not a substrate for COX-1,

presence and amount of PGH₂-EA metabolites "relates" to the activity of the COX-2 enzyme.

Applicants also argue that Yu et al. fail to disclose or suggest a method whereby detection from a sample of a subject and quantification of the results is indicative of an activity of a COX-2 enzyme. Examiner respectfully disagrees. Yu et al. does teach a method that "relates the amount of PGH₂-EA metabolites to the activity of the COX-2 enzyme in the subject", mammalian cell, since detection and quantification of PGH₂-EA metabolites is indicative of COX-2 activity.

Applicants also argue that Yu et al. fails to disclose or suggest the connection between PGE₂ to COX-2 activity, its presence, and the significance of its presence. Examiner respectfully disagrees. Yu et al. does teach a method of detecting/measuring activity of COX-2 by detecting PGH₂-EA metabolites (abstract and Figures 2-6). Yu et al. clearly teaches that PGE₂ are substrates of COX-2 (Figures 2-6 and page 21182, right column, page 21183, right column, page 21184, right column and page 21186, left column).

Applicants also argue that the present invention provides significant advantages over the prior art, such as the ability to detect and/or quantify COX-2 directly in the patient. The argument is moot because the claims do not recite a step of detecting or quantifying COX-2 directly in the living subject, but detecting PGH₂-EA metabolites from a sample obtained from a living subject.

Hence the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 6-21 and 55-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu et al. in view of Tsujii et al.

Claims 6-21 and 55-60 drawn to a method of obtaining a sample from a living subject, such as urine, detecting/measuring an amount of PGH₂-EA metabolites, relating the amount measure to the activity of the COX-2 enzyme and/or relating the

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amount of the metabolites to a disease state or progression of a disease state, such as cancer/tumor.

The reference of Yu et al. as it applies to claim 4 teaches a method of detecting/measuring COX-2 in a sample by detecting/measuring a PGH2-EA metabolites (Figures 2-6 and pages 21182), as discussed above. Yu et al. also teaches generating a standard value and curve for determining COX-2 activity (Figure 1 and Table 1) and detecting/measuring COX-2 activity by detecting PGH2-EA metabolites via a mass chromatogram (Figures 3-5) and immunoassays (Figure 2 and Figure 6).

The difference between the reference of Yu et al. and the instant invention is that the reference of Yu et al. does not teach a step of relating the amount of the metabolites to a disease state or progression of a disease state, such as cancer/tumor, or by obtaining an urine sample from a subject.

However, it is well established and known in the art that COX-2 expression is increased in cancerous cells, such as in colon cancer cells, as disclosed by Taketo et al. (reference BK: form PTO-1449). With this knowledge in hand, one having ordinary skill in the art would have concluded to apply the method of Yu et al. to relate the amount of PGH2-EA metabolites and thereby COX-2 activity to disease state or progression of a disease state, such as colon cancer, by obtaining a sample from a subject, such as an urine or blood sample.

Therefore, combining the teachings of Yu et al. and Taketo et al., it would have been obvious to one having ordinary skill in the art to apply the method of Yu et al. in following the progression of colon cancer or to monitor colon cancer in a subject. One

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of ordinary skill in the art would have been motivated to combine the references in order to follow the progression or monitor colon cancer in a subject. One of ordinary skill in the art would have had a reasonable expectation of success since Yu et al. successfully teaches selective detection/measurement of COX-2 activity in a sample and Taketo et al. teaches that COX-2 expression and thereby activity of COX-2 is increased in colon cancer cells in subjects.

Therefore, the above references render claims 6-21 and 55-62 *prima facie* obvious to one of ordinary skill in the art.

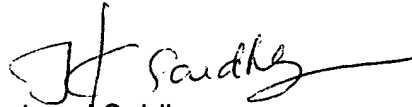
None of the claims are in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652


Tekchand Saidha
Primary Patent Examiner 1652

**TEKCHAND SAIDHA
PRIMARY EXAMINER**